DETAILED ACTION

1. This Office Action is in response to Applicant's amendments and remarks filed 7/28/08.

2. Claims 1, 25, 32, 43 and 44 have been amended. Claims 1, 3-11, 25, 27-30, 32-39, 43 and 44 are pending and examined.

Claim Rejections - 35 USC § 103, maintained

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3a. The rejection of claims 1, 3-11, 25, 27-30 ad 32-39 and 43-44 under 103(a) as unpatentable over Morton et al. (WO 95/15338) in view of the M.S. study (Neurology, 1993) is maintained for reasons of record in the Office Actions dated 5 August 2003, 5 October 2004, 27 April 2005, 1 February 2006 and 16 June 2006, 19 January 2007 and 28 July 2008.

The claims require treating multiple sclerosis by administering cpn10 and IFN-β, wherein the therapeutic effect of administering cpn10 and a suboptimal amount of IFN-β together is improved therapeutic effect compared to that of administering the same equivalent amount of cpn10 or IFN-β alone. Applicants assert that neither the Morton reference nor the MS study, nor the combination thereof, teaches or suggests that combined cpn10 and IFN-β treatment of MS or delay the relapse following cessation of other treatments. It is asserted that the administration of a drug at doses which, if not administered in combination with a second, different drug, would be ineffective, is a significantly different fact pattern than "optimizing" an otherwise clinically effective dose. Further, it is argued that Morton (WO 95/15338), does not teach or suggest administering IFN-β to patients at clinically ineffective dosages. It is also asserted that there is no motivation to combine the cited references Morton and the MS study in this obviousness rejection. Applicant's arguments have been fully considered but are not found to be persuasive.

Applicant has modified the claims to include IFN-β amounts that are clinically ineffective amount. Applicant asserts that the invention provides methods of treating MS in an individual taken off IFN-β treatment or having reduced dose IFN-β treatment because of IFN-β-induced side effects, by administering to an individual in need thereof a combination treatment comprising pharmaceutically effective amounts of both cpn10 and IFN-β, wherein the IFN-β is administered at a dose that does not produce IFN-β induced side effects in the individual. As argued previously in the Office Action dated 6/16/2006 (pages 4-5) the dosages of cpn10 and IFN-β disclosed in Morton et al. and the MS study are within the doses contemplated in the instant invention. For example, Morton on page 27 discloses cpn10 doses of 1-1000μg/kg of body weight and more preferably 50-200μg/kg of body weight encompasses the 10-30 mg of cpn10 contemplated in the instant invention. In addition, the IFN-β doses disclosed in the MS study group (1.6 MIU and 8 MIU) are similar to those contemplated in the instant invention.

Applicant argues that administering a drug at dosages, which, if not administered in combination with a second, different drug, would be ineffective (clinically), is a significantly different fact pattern than "optimizing" an otherwise clinically effective dose to effective dosages. Applicant further contends that administering a drug at a clinically ineffective dose is not merely "optimizing a workable range" by routine experimentation. The MS study group used 1.6MIU and 8MIU, which is within the "clinically ineffective dose" contemplated by the Applicant (1-10MIU). Furthermore, the 1.6MIU of IFN-β used in the MS study is much lower than 4-6MIU recited in the claims and less than optimum

compared (suboptimal) to 8MIU administration (page 660). The MS study also discloses that 16MIU produced unacceptable toxicity (page 660). Therefore, *In re Aller* fact pattern is applicable to the administration of IFN-β because it is routine in the art to optimize the dosage administered to a patient obtain optimal clinical outcome and thus not inventive.

Applicant argues that the range of dosages contemplated by the MS study is not relevant because the MS study taught ranges that were clinically relevant in contrast to those of the instant invention which if administered alone will not be effective. However, this argument is not persuasive because the lower doses contemplated by the instant invention (supposed to be suboptimal) were clearly disclosed by the MS study (see also discussion above). Further, the rationale for combination treatment was discussed previously. Therefore the rejection of record is maintained.

4. New rejections necessitated by Applicant's amendment.

Claim Rejections - 35 USC § 112, second paragraph (New)

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 3-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5a. Claim 1 are rejected as vague and indefinite for reciting the term "suboptimal" is not defined in the specification. The artisan would be unable to determine what amounts Applicants intended the claims to encompass. The amounts contemplated to be “suboptimal” (that is the dose that is ineffective if administered alone) is disclosed in the prior art (MS study) to be effective. Therefore, it is not clear what doses would be considered “suboptimal” (i.e. ineffective if administered alone) because the recited dosages in the specification do not meet this limitation as evidenced by the prior art. Claims 3-11are rejected insofar as they are dependent on rejected claim 1.

Claim Rejections - 35 USC § 112, first paragraph (New)

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6a.Claims 1, 3-11, 27, 28, 29, 30, 33, 34, 35, 36, 37, 38, and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a new matter rejection.*

The recitation of “suboptimal amount of IFN-β that is not effective if administered alone to the individual” has no support in the specification. Although Applicant in the

response filed 7/28/09 (page 7) indicates that the support for the claim language is found at page 13, lines 3-6, the disclosure at page 13, lines 3-6 discloses that IFN-β might be ineffective or sub-optimal. There is no disclosure of suboptimal amounts of IFN-β that is not effective if administered alone to the individual. The Applicant is required to cancel the new matter in the reply to this Office Action.

6b. Claims 1, 3-9, 27, 28, 29, 30, 33, 34, 35, 36, 37, 38, and 39 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims require treating multiple sclerosis by administering cpn10 and IFN-β, wherein the therapeutic effect of administering cpn10 and a suboptimal amount of IFN-β together is improved therapeutic effect compared to that of administering the same equivalent amount of cpn10 or IFN-β alone. The specification does not teach what the suboptimal dose of IFN-β is. However, the specification teaches that the pharmaceutically-effective amount of IFN-β is 1-10 million international units (MIU) of IFN-β (page 13, lines 11-15). It further teaches that the preferable amount is 4-6 MIU of IFN-β. The prior art (MS study) teaches that 1.6 MIU and 8 MIU are functional. Therefore, it is not clear what suboptimal doses can be used for treatment. Thus, the Applicant's have not fully described the genus of IFN-β amounts to be used in the treatment of MS.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of the amount considered to be suboptimal for the treatment of MS. For example, the teaching may include the amount of IFN-β per Kg required for the treatment. In this case, the only factor present in the claims is a requirement that the IFN-β used is suboptimal. There is no disclosure of any particular amount of IFN-β to be used for the treatment of MS that could be considered suboptimal because the prior art doses. Accordingly, in the absence of sufficient disclosure the specification does not provide adequate written description of the claimed genus.

6c. Claims 1, 3-9, 27, 28, 29, 30, 33, 34, 35, 36, 37, 38, and 39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention of treating MS using suboptimal amounts of IFN-β that does not produce IFN-β-induced side effects in the individual.

The factors to be considered when determining if the disclosure satisfies the enablement requirement have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breath of

claims. Ex Parte Forman, (230 USPQ 546 (Bd. Pat. App. & Int. 1986); In re Wands, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

The specification, on page 13 lines 3-6 discloses that IFN-β might be ineffective or sub-optimal. The specification, on page 13, teaches that the pharmaceutically-effective amount of IFN-β is 1-10 million international units (MIU) of IFN-β (page 13, lines 11-15). It further teaches that the preferable amount is 4-6 MIU of IFN-β. Thus, the breadth of the claims is excessive because the specification does not teach the suboptimal amounts contemplated in the specification. However, the prior art teaches using 1.8 MIU and 8 MIU. There is no guidance or examples in the specification that teach the use of suboptimal amounts of IFN-β used in the treatment of MS. A person of ordinary skill in the art would not be able to predict which of the many possible suboptimal amounts would treat MS without side effects.

In summary, due to the excessive breadth of the claims, the lack of guidance or examples in the specification which teaches administration of suboptimal amounts of IFN-β, and unpredictability in the art regarding the various amounts used for the treatment without side effects, a person of ordinary skill in the art would require further, undue experimentation to make and use the instant invention.

Conclusion

7. No claims are allowable.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon, Ph.D whose telephone number is 571-272-0892. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao, Ph. D can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

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/Christine J Saoud/
Primary Examiner, Art Unit 1647